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Reduction of (1,3-diene)tricarbonyliron(0) complexes: application to (ergosterol acetate)tricarbonyliron(0)

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Abstract

Reaction of (ergosterol acetate)tricarbonyliron(0) (**1**) with lithium aluminiumhydride leads to the selective reduction of the 5,6 double bond. The A/B ring junction of the reduction product has been shown to be *trans* on the basis of ^{13}C NMR. This information has been used to confirm that the initial addition of hydride to the coordinated ergosterol acetate occurs on the α-face at C-5. © 1997 Elsevier Science S.A.

Keywords: (Ergosterol acetate)tricarbonyliron(0); Reduction; Deuteration

1. Introduction

In recent papers we reported that reaction of lithium aluminiumhydride with tricarbonyliron(0) complexes of 1-azabuta-1,3-dienes, 1-oxabuta-1,3-dienes and homo-1,3-dienes leads to the formation of saturated amines, alcohols and hydrocarbons respectively in good yield [1,2]. When lithium aluminiumdeuteride is used for these reactions, the products have been shown to contain three deuterium atoms [1,2]. In this paper we describe the application of this chemistry to (ergosterol acetate)tricarbonyliron(0) (**1**) and show how the products illustrate the relative stereochemistry of the hydride addition reaction at C-5 of the coordinated steroid.

2. Results and discussion

Initially the reaction between (ergosterol acetate)tricarbonyliron(0) (**1**) and lithium aluminiumhydride was studied. Complex (**1**) was obtained by warming ergosterol acetate (**2**) with (2-methyl-4-phenyl-1-oxabuta-1,3-diene)tricarbonyliron(0) (**3**) in accordance with literature procedures [3]. The yellow crystals obtained were identified as (ergosterol acetate)tricarbonyliron(0) (**1**) by comparison of their spectroscopic data with literature values [3–5]. The yield of this reaction was significantly improved by addition of triiron dodecacarbonyl to the reaction mixture. We suggest that addition of the triiron dodecacarbonyl to the reaction enables rapid regeneration of the transfer reagent (**3**) during the reaction which significantly improved the yield of steroid complex (**1**) (Scheme 1).

A solution of complex (**1**) in diethyl ether was added at 0°C to a suspension of an excess of lithium aluminiumhydride in diethyl ether and the resulting mixture was stirred at 0°C for 3 h, was quenched with methanol and the mixture was allowed to warm to 25°C. Filtration and chromatography lead to a yellow solid identified as (ergosterol)tricarbonyliron(0) (**4**) by comparison of the spectroscopic data with those quoted in the literature [6]. There was no evidence for any other product in the reaction mixture.

Although the reaction between (1,4-diphenylbuta-1,3-diene)tricarbonyliron(0) with lithium aluminiumhydride under identical conditions leads to partial reduction and formation of 1,4-diphenylbut-1-ene [2], the 5,7-diene fragment of the steroid complex (**1**) is unreactive under these reaction conditions so that only the selective reduction of the acetate function is observed, presumably because of the highly hindered nature of the 5,7-diene system.

A solution of complex (**1**) in diethyl ether was heated at reflux for 3 h with a suspension of lithium aluminiumhydride in diethyl ether. White crystals were pro-

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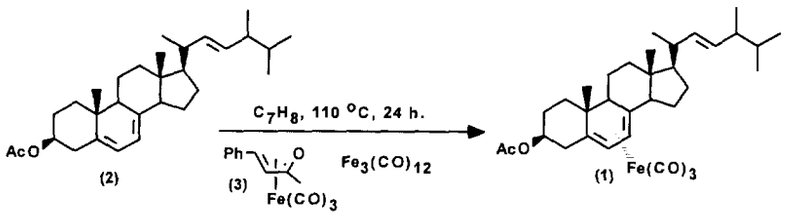


Scheme 1.

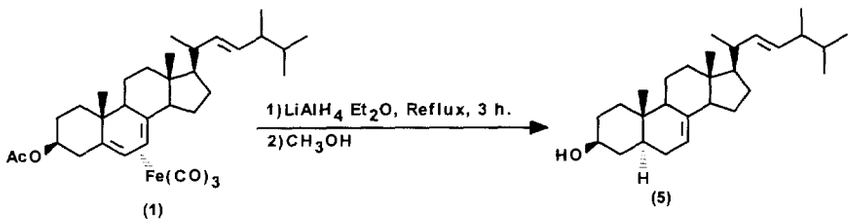
duced after a standard work-up. These crystals were 5α-ergosta-7,22-diene-3β-ol (**5**) (^{13}C NMR spectrum [7], and m.p. [8,9]). There was no evidence (300 MHz ^{1}H and 75 MHz ^{13}C NMR) of reduction of the 7,8-or 22,23-double bonds (Scheme 2).

All attempts to furnish the reduction of the entire 5,7-diene system (e.g., by changing solvents, reaction temperatures, quantity of reducing agent etc.) failed. Other workers similarly could not achieve this using a range of reagents and reaction conditions [8–11]. In each case the lack of reaction at the 7,8-double bond was attributed to steric factors.

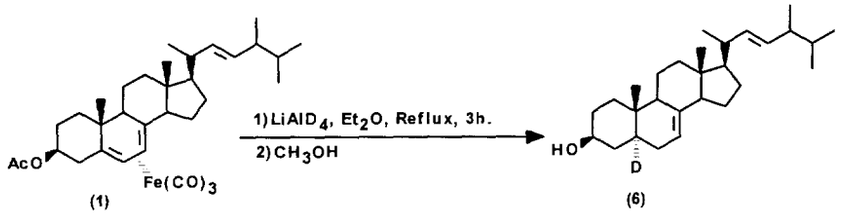
Further information about the reduction of (ergosterol acetate)tricarbonyliron(0) (**1**) was found from deuteration experiments. Reaction of complex (**1**) with lithium aluminiumdeuteride at reflux for 3 h followed by a protic quench and chromatography lead to isolation of the deuterated steroid (**6**). The deuterium incorporation in this case only occurred at C-5 as indicated by the presence of a 1:1:1 triplet at 40.47 ppm (^{13}C NMR spectrum) and at 1.15 ppm (H-5α; ^{2}H NMR) (Scheme 3).

When the reaction was performed using lithium aluminiumhydride and quenched with a deuterium source under the same conditions, the ^{13}C NMR spectrum of the reaction product (**7**) contained a 1:1:1 triplet due to C-6 (29.62 ppm) and a signal at 1.61 ppm in the ^{2}H NMR spectrum (H-6) (Scheme 4).

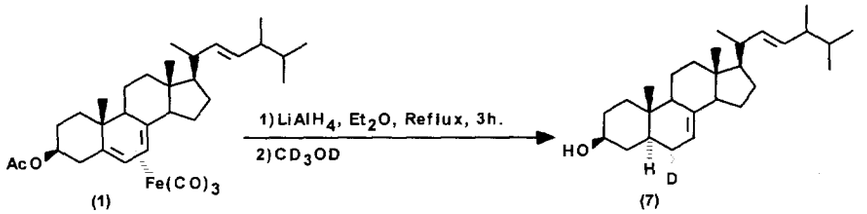
When lithium aluminiumdeuteride was used for the reduction and a deuterium source was used for the



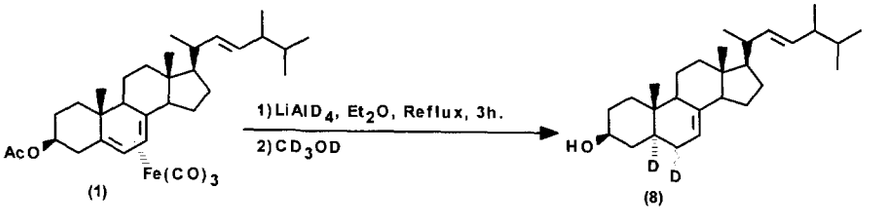
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

quench, the ^{13}C NMR spectrum contained a pair of 1:1:1 triplets at 40.47 and 29.62 ppm corresponding to C-5 and C-6 of the 5,6-dideutero steroid (**8**) (Scheme 5).

The A/B ring junction of the reduction product (**5**) was confirmed as *trans* since the extra shielding of the C-19 methyl group from steric compression with the protons at C-2 and C-4 causes its ^{13}C NMR signal to appear at 12–15 ppm. The *cis* A/B ring, where this interaction with the protons at C-2 and C-4 is not present, shows the ^{13}C signal at 20–25 ppm region [12–14] (Scheme 6).

In reaction product (**5**) the signal due to the methyl group C19 occurs at 13.03 ppm which is in the region expected for the *trans* A/B ring junction. On the basis of these assignment it is reasonable to conclude that the reaction product (**5**) contains a *trans* ring junction.

Formation of a *trans* A/B ring junction may be explained in terms of overall addition of hydride to the α-face of the coordinated steroid. Direct addition of hydride to either C-5 or C-6 of the coordinated steroid is unlikely owing to the bulk of the tricarbonyliron(0) [15]. It therefore seems likely that the reaction proceeds by initial attack by hydride at a coordinated iron carbonyl ligand to yield a iron formyl intermediate (**9**) [16]. Addition of hydride to (buta-1,3-diene)tricarbonyliron(0) has been previously studied and has been shown to occur by formation of an anionic iron formyl intermediate. This type of intermediate has been shown to transfer hydride to a terminal position of the coordinated 1,3-diene to yield an anionic (η^3-allyl)tricarbonyliron(0) complex [16].

In the case of the reaction between (ergosterol acetate)tricarbonyliron(0) (**1**) and lithium aluminiumhydride formation of iron formyl intermediate (**9**) can be used to rationalise the stereochemistry observed at C-5 in the reduction product (**5**). Transfer of hydride from formyl complex (**9**) is likely to occur on the α-face of the coordinated ergosterol and lead to formation of the anionic η^3-allyl intermediate (**10**). Protonation of (**10**) at C-6 leads to fomation of reaction product (**4**) containing a *trans* A/B ring junction (Scheme 7).

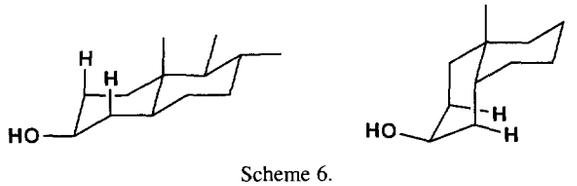
The results from this work have shown that reaction of lithium aluminiumhydride with (ergosterol acetate)tricarbonyliron(0) leads to reduction of the 5,6 double bond of ergosterol. Addition of hydride to the coordinated ergosterol occur on the α-face of C-5 and the quench occurred at C-6 although the stereochemistry of the quench cannot be determined.

3. Experimental

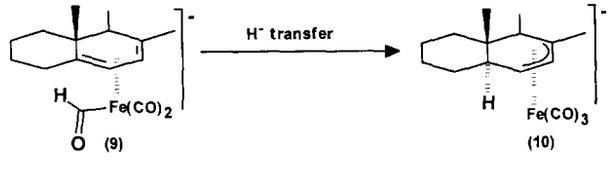
All reactions under an atmosphere of nitrogen were performed using standard vacuum and Schlenk line techniques [17]. Diethyl ether was dried over lithium aluminiumhydride and was distilled, toluene was dried over sodium metal and was distilled. Ergosterol acetate (**2**) was synthesised from ergosterol in accordance with a literature procedure [18]. Melting points were recorded on a Kofler hot stage micro-melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 300 instrument at 300 MHz and 75.4 MHz respectively. All chemical shifts are quoted in parts per million relative to a tetramethylsilane standard. Flash chromatography was performed on Merck (40–63 μm) silica. Filtration's on alumina were performed using deactivated Brockmann (grade iv) alumina. Elemental analyses were performed on an Leeman Laboratories CE 477 instrument.

3.1. Synthesis of (ergosterol acetate)tricarbonyliron(0) (1)

(2-Methyl-4-phenyl-1-oxabuta-1,3-diene)tricarbonyliron(0)(**3**), (0.25 g, 0.86 mmol) and triiron dodecacarbonyl (0.45 g, 0.86 mmol) ergosterol acetate (**2**) (0.33 g, 0.84 mmol) were stirred in toluene at 110°C for



Scheme 6.



Scheme 7.

24 h under an atmosphere of nitrogen. The resulting mixture was filtered through alumina and the solvent removed under reduced pressure to give a yellow gum. This gum was chromatographed on silica gel using petroleum ether/ethyl acetate (20:1). The eluent was evaporated and the product was digested in methanol. Unreacted ergosterol acetate (**2**) was removed as a precipitate and the resultant solution was left to stand at −20°C overnight, whereupon the complex (**1**) crystallised, (0.20 g, 42%). M.p. 94–95°C (Lit. [5], 95–99°C); ν_{max}. (Nujol) 1 945s (C≡O) 2 025s (C≡O) and 1 735 cm^{-1} s (C=O ester), (Lit. [5], (Nujol) 1 950s (C≡O) 2 030s (C≡O) and 1 730 cm^{-1} (C=O ester); δ_H (300 MHz; $CDCl_3$) 0.71 (3H, s, 18-Me), 0.82 (6H, 2 × d, *J* 6.3 Hz, 26-and 27-Me), 0.89 (3H, d, *J* 6.2 Hz, 28-Me), 0.91 (3H, s, 19-Me), 0.99 (3H, d, *J* 6.6 Hz, 21-Me), 2.02 (3H, s, 30-Me), 2.34 (1H, t, *J* 12.8 Hz, 4β-*H*), 4.73 (1H, m, 3α-*H*), 4.88 (1H, d, *J* 4.1 Hz, 7-*H*), 5.17 (2H, m, 22-and 23-*H*), 5.22 (1H, d, *J* 4.2 Hz, 6-*H*). (Lit. [4], H(500 MHz; $CDCl_3$) 0.70 (18-Me), 0.80 (27-Me), 0.82 (26-Me), 0.89 (28-Me), 0.90 (19-Me), 0.99 (21-Me), 1.85 (30-Me), 2.15 (4β-*H*), 4.72 (3α-*H*), 4.88 (7-*H*), 5.17 (22-and 23-*H*), 5.20 (6-*H*)).

3.2. Reaction of (Ergosterol acetate)tricarbonyliron(0) (1) with lithium aluminiumhydride at reflux.

To a solution of (ergosterol acetate)tricarbonyliron(0) (**1**) (0.10 g, 0.18 mmol) in diethyl ether (5 ml) at 0°C was added dropwise a suspension of lithium aluminiumhydride (0.066 g, 1.70 mmol) in diethyl ether at 0°C. The resulting mixture was heated at reflux for 3 h under an atmosphere of nitrogen. The reaction mixture was cooled to room temperature and was filtered through a plug of alumina to remove the solid residues then allowed to warm to room temperature. The reaction was quenched with methanol and the dark mixture produced was slurried with alumina and filtered. The solvent was removed under reduced pressure to yield a yellow gum which was identified as 5α-ergosta-7,22-diene-3β-ol (**5**) by comparison of its ^1H NMR and ^{13}C NMR spectra with literature values (0.044 g, 65%). M.p. 175–177°C (Lit. [8,9], 176–177°C); δ_H ($CDCl_3$ 300 MHz) 3.59 (1H, m, 3α), 5.19 (3H, m, 22- and 23*H* and 7-*H*); δ_C (75 MHz; $CDCl_3$) 12.07 (C-18), 13.02 (C-19), 17.59 (C-28), 19.63 (C-21), 19.94 (C-26), 21.52 (C-27), 21.47 (C-11), 22.91 (C-15), 28.09 (C-16), 29.62 (C-6), 31.45 (C-2), 33.07 (C-25), 34.08 (C-10), 37.12 (C-1), 37.96 (C-4), 39.43 (C-12), 40.24 (C-5), 40.47 (C-20), 42.77 (C-4), 49.43 (C-9), 55.09 (C-14), 55.94 (C-17), 71.03 (C-3), 117.44 (C-7), 131.86 (C-22), 135.65 (C-23), and 139.56 (C-8); (Lit. [7], δ_C (25 MHz; $CDCl_3$) 12.1 (C-18), 13.0 (C-19), 17.5 (C-28), 19.6 (C-21), 19.9 (C-26), 21.1 (C-27), 21.5 (C-11), 22.9 (C-15), 28.1 (C-16), 29.6 (C-6), 31.4 (C-2), 33.0 (C-25), 34.1 (C-10), 37.1 (C-1), 37.9 (C-4), 39.4 (C-12), 40.2 (C-5), 40.4 (C-20), 42.7 (C-24), 43.1 (C-13), 49.4 (C-9), 55.0 (C-14), 55.8 (C-17), 70.8 (C-3), 117.1 (C-7), 131.4 (C-22), 135.2 (C-23), 139.0 (C-8)).

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